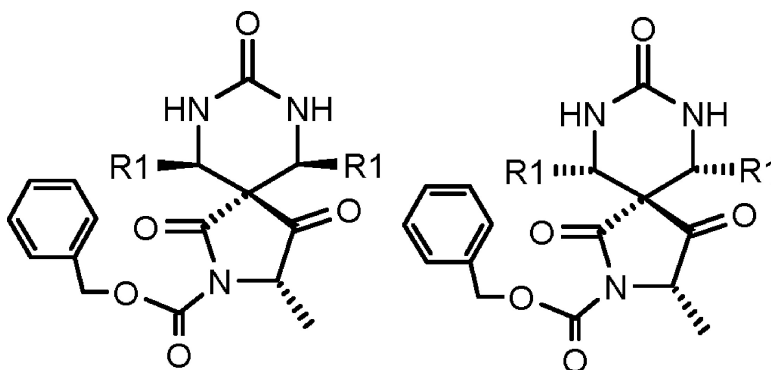Article

Anomalous Regioselective Four-Member Multicomponent Biginelli Reaction II: One-Pot Parallel Synthesis of Spiro Heterobicyclic Aliphatic Rings

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Anomalous Regioselective Four-Member Multicomponent Biginelli Reaction II: One-Pot Parallel Synthesis of Spiro Heterobicyclic Aliphatic Rings

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In a previous preliminary study, we found that a cyclic five-member ring β-keto ester (lactone) reacts with one molecule of urea and two of aldehyde to give a new family of spiro heterobicyclic aliphatic rings in good yields with no traces of the expected dihydropyrimidine (Biginelli) products. The reaction is driven by a regiospecific condensation of two molecules of aldehyde with urea and β-keto-γ-lactone to afford only products harboring substitutions exclusively in a syn configuration (Byk, G.; Gottlieb, H. E.; Herscovici, J.; Mirkin, F. *J. Comb. Chem.* **2000,** *2,* 732−735). In the present work ((a) Presented in part at ISCT Combitech, October 15, 2002, Israel, and Eurocombi-2, Copenhagen 2003 (oral and poster presentation). (b) Also in American Peptide Society Symposium, Boston, 2003 (poster presentation). (c) Abstract in *Biopolymers* **2003***, 71* (3), 354−355), we report a large and exciting extension of this new reaction utilizing parallel organic synthesis arrays, as demonstrated by the use of chiral β-keto-γ-lactams, derived from natural amino acids, instead of tetronic acid (β-keto-γ-lactone) and the potential of the spirobicyclic products for generating "libraries from libraries". Interestingly, we note an unusual and important anisotropy effect induced by perpendicular interactions between rigid π systems and different groups placed at the α position of the obtained spirobicyclic system. Stereo/regioselectivity of the aldehyde condensation is driven by the nature of the substitutions on the starting β-keto-γ-lactam. Aromatic aldehydes can be used as starting reagents with good yields; however, when aliphatic aldehydes are used, the desired products are obtained in poor yields, as observed in the classical Biginelli reaction. The possible reasons for these poor yields are addressed and clarify, to some extent, the complexity of the Biginelli multicomponent reaction mechanism and, in particular, the mechanism of the present reaction. Finally, we have investigated and proposed a mechanism for this new reaction by intercepting several intermediates.

Introduction

Drug discovery techniques have dramatically evolved from the beginning of the 1990s. Together with the genomics and proteomics sciences, whose main goal is to discover new pharmacological targets for treating human deseases, a significant improvement in pharmaceutical targets discovery and screening techniques were reached by applying automated techniques. This automation brought about the ability to screen small molecules at a rate of up to 1 000 000 molecules/day.[3]

A substantial change in synthetic methods is, therefore, crucial to match the thoughput of automation in biological screening techniques. Modern synthetic methods should be adapted so that a large diversity and number of molecules can be obtained in a short period of time. Novel fast synthetic methods are currently being developed in many synthetic groups.[4] Among these methods, multicomponent reactions are of special interest because they can generate in a single reaction complex molecules, such as hetero aliphatic and hetero aromatic polycyclic rings, and can be adapted to parallel automated synthesis. Special attention was devoted to the multicomponent Biginelli reaction, whose possible mechanism and extensions were reinvestigated during the past decade.[5−8]

A main goal in our laboratory is to discover and develop novel reactions for extending the scope of combinatorial chemistry. Specifically, multicomponent reactions are of great interest for high-throughput synthesis, because the different components can be automatically fed onto a robot, and products are obtained in one pot.

While searching for new extensions of the Biginelli reaction, we have recently discovered an anomalous extended MCR4 (multicomponent reaction of four members) Biginelli reaction.[1] This reaction proceeds in a regioselectively directed tandem reaction that results exclusively in a 1:1 mixture of two syn isomers, as shown in Figure 1.

Here, we have extended this new reaction to the condensation between cyclic β-keto lactams (**1** in Figure 2) derived from amino acids with two molecules of aldehyde and urea (see Figure 2). The new molecules (**2** or **3**, Figure 2) discovered by this new Biginelli variant can also potentially

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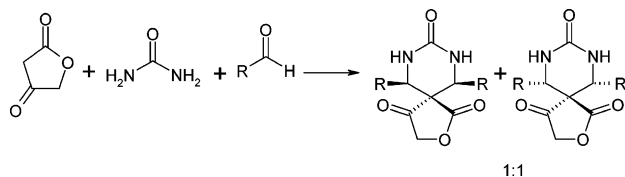
Figure 1. Generation of spiroheterobicyclic structure by a multi-component reaction MCR4.
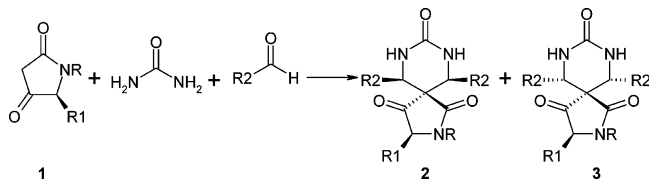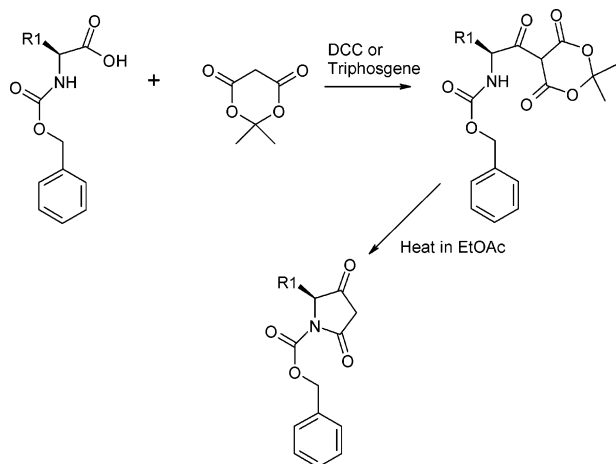

Figure 2. Extension of MCR4 to β-keto-γ-lactam.

Scheme 1

be further elaborated to increase available diversity according to the "libraries from libraries principle".[9]

Figure 3. Synthesis of the spirobicyclic rings and side products.

acted both as solvent and catalyst, and heating only at 60–80 °C (heating at 120 °C produced significant quantities of Knoevenagel product).

We thus synthesized series of representative spirobicyclic rings derived from glycine (products **1a–g**), alanine (products **2a–g**), and phenylalanine (products **3a–f**), with aromatic aldehydes (see Table 1). In general, the reaction proceeds regioselectively (only syn products are obtained) and also partially stereoselectively (when chiral lactams are used as precursors, three new asymmetric carbons are generated and the ratio between the two obtained stereoisomers varies, depending on the side chain of the lactam). Unlike the previously reported spirolactones that were obtained in 1:1 mixtures,[1] the present lactams bear a benzyloxycarbonyl group on the lactam nitrogen. This group induces a selectivity that favors the generation of one of the syn isomers, as seen by HPLC and NMR analysis of products obtained from α-unsubstituted β-ketolactam (obtained from glycine). Isomer ratios varied between 3:2 for products **1e/1e′** up to 3:1 for products **1b/1b′**. When lactams where substituted on the α-position (alanine and phenylalanine derivatives), the selectivity varied between 1.25:1 for products 3e/3e′ up to 3.5:1 for products 2b/2b′. It should be pointed out that in the case of chiral β-ketolactams, the products are obtained stereoselectively as mixtures of only two diastereoisomers bearing three asymmetric carbons. To date, we are not able to explain systematically the stereo-selectivity observed for the different products, and studies are being performed to elucidate this point. Finally, a very curious anisotropic effect is observed for the α-methyl or α-methylene groups from alanine and phenylalanine as a result of a strong perpendicular interaction between the fixed π electrons of the aromatic groups and these hydrocarbons (for example, a displacement of 1.18 ppm was observed for product **2a** and 1.6 ppm for product **3a**, as compared to the expected values of 1.46 and 3.1 ppm, respectively). On the other hand, electron-withdrawing groups placed at the 4-position on the aryl functions diminishes this particular anisotropic effect, presumably as result of a lowering of the π-electron density in the aromatic rings (for example, products **2b/f/g**). The effect is similar in both stereomers along the series. For example, **2a** and **2a′** had values of 0.28 and 0.44, respectively. These results can be rationalized building a molecular model of both isomers; it appears that the methyl groups in both isomers are very close to the π-cloud of one of the phenyl groups placed (in both isomers) in the equatorial position on the chair configuration of the

Results and Discussion

The starting β-keto-γ-lactams can be obtained by a method previously reported[10] that we have improved here but that needs chromatographic purification or by a new method developed here using the simple and inexpensive new coupling reagent triphosgene, recently proposed by Gilon et al.[11] We found it to be very convenient because the obtained crude lactams do not need further purification prior to use (see Scheme 1).

To maintain full protection during heat-mediated reactions, the best choice was the use of *N*-benzyloxycarbonyl lactams. This protection can be easily removed after condensation or further modifications.

The optimal reaction conditions for the multicomponent reaction were established after several attempts to obtain the products using different reagent ratios, concentrations, catalysts, and temperatures. Briefly, the main competing side reaction was the generation of a Knoevenagel product obtained by the reaction of the lactam with 1 equiv of aldehyde (Figure 3). This reaction is usually base-catalyzed; however, the high acidity of the α-protons in the lactams allowed this side reaction also under acidic conditions. We could prevent this side reaction by reducing the amount of aldehyde, changing the acid catalyst to acetic acid, which
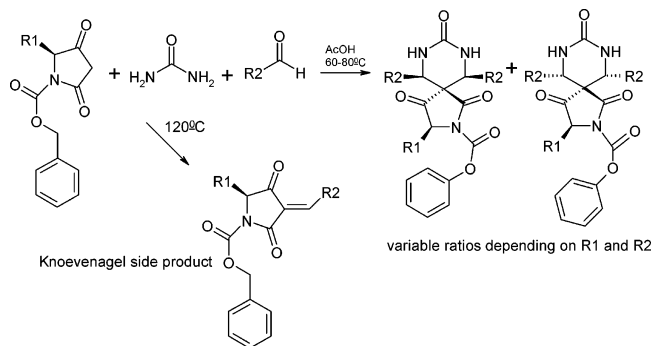
Table 1. Spirobicyclic Products Obtained, Their Yields and Characterization

Z= benzyloxycarbonyl   1-3a-g   1-3a'-g'

no.	R_1	R_2	X	yield %	quantity g	calcd mass	MH$^+$	HRMS
1a[a]	Ph	H	O	75	0.150	469.1637	470	469.1623
1b[a]	(*p*-Cl)Ph	H	O	70	0.161	539.1014	540	539.0966
1c[a]	(*p*-CH$_3$)Ph	H	O	80	0.170	497.1950	498	497.1880
1d[a]	(*p*-OH)Ph	H	O	53	0.11	502.1614	503	502.1661
1e[a]	(*p*-OCH$_3$)Ph	H	O	85	0.190	529.1849	530	529.1781
1f[a]	(*p*-NO$_2$)Ph	H	O	75	0.180	559.1379	560	559.1371
1g[a]	(*p*-F)Ph	H	O	70	0.151	505.1449	506	505.1446
2a	Ph	CH$_3$	O	50	0.390	484.1872	484	484.1875
2a'	Ph	CH$_3$	O	25	0.191	484.1872	484	484.1875
2b	(*p*-Cl)Ph	CH$_3$	O	42	0.354	552.1093	552	552.1054
2b'	(*p*-Cl)Ph	CH$_3$	O	22	0.187	552.1093	552	552.1054
2c	(*p*-CH$_3$)Ph	CH$_3$	O	54	0.446	512.2185	512	512.2203
2c'	(*p*-CH$_3$)Ph	CH$_3$	O	20	0.165	512.2185	512	512.2203
2d[a]	(*p*-OH)Ph	CH$_3$	O	55	0.457	515.1692	516	515.1718
2e	(*p*-OCH$_3$)Ph	CH$_3$	O	63	0.553	544.2083	544	544.2020
2e'	(*p*-OCH$_3$)Ph	CH$_3$	O	31	0.272	544.2083	544	544.2020
2f[a]	(*p*-NO$_2$)Ph	CH$_3$	O	63	0.576	574.15740	574	574.1563
2g[a]	(*p*-F)Ph	CH$_3$	O	60	0.504	520.1691	520	520.1684
3a	Ph	Bn	O	42	0.0726	559.2107	560	559.2098
3a'	Ph	Bn	O	40	0.069	559.2107	560	559.2098
3b	(*p*-Cl)Ph	Bn	O	41	0.8	628.1406	628	628.1439
3b'	(*p*-Cl)Ph	Bn	O	20	0.4	628.1406	628	628.1439
3c	(*p*-CH$_3$)Ph	Bn	O	40	0.072	587.2420	588	587.2453
3c'	(*p*-CH$_3$)Ph	Bn	O	40	0.072	587.2420	588	587.2453
3d	(*p*-OCH$_3$)Ph	Bn	O	42	0.8	620.2396	620	620.2331
3d'	(*p*-OCH$_3$)Ph	Bn	O	33	0.64	620.2396	620	620.2331
3e[a]	(*p*-NO$_2$)Ph	Bn	O	25	0.5	650	650	
3f[a]	(*p*-F)Ph	Bn	O	51	0.9	595.1918	596	595.1874
3f	(*p*-F)Ph	Bn	O	12	0.22	595.1918	596	595.1874

[a] Isolated as mixture of two syn diastereomers.

Scheme 2
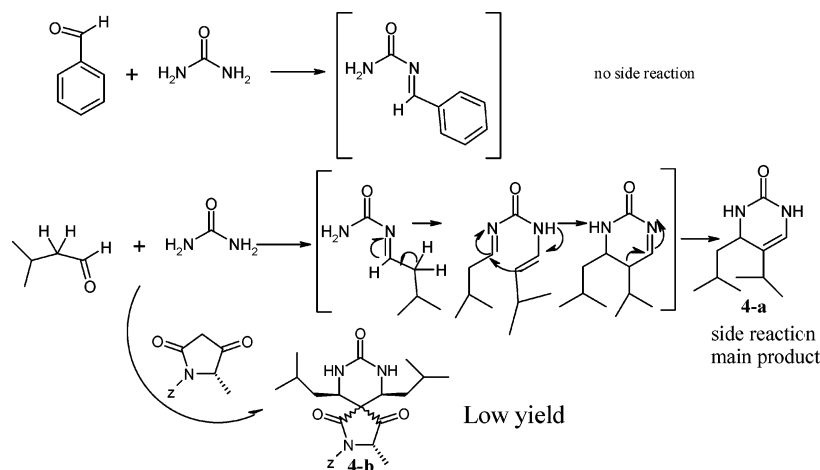
scaffolds. The distance between the center of the aromatic ring and the carbon atom of the methyl group is ∼2.5 Å for **2a** and 3 Å for **2a'**, which explains both the anisotropic effect and the similar chemical shift observed for both isomers.

The efficiency of the reaction was detrimentally affected by the presence or absence of α-protons in the starting aldehyde. Aromatic aldehydes generated products in high yields (50−90% of isomer mixtures), while aliphatic aldehydes resulted in very poor yields (5−15%) (see product **4b** in Scheme 2) in full agreement with previous reports for the regular Biginelli reaction. We have specifically studied the condensation with isovaleraldehyde. We have found that
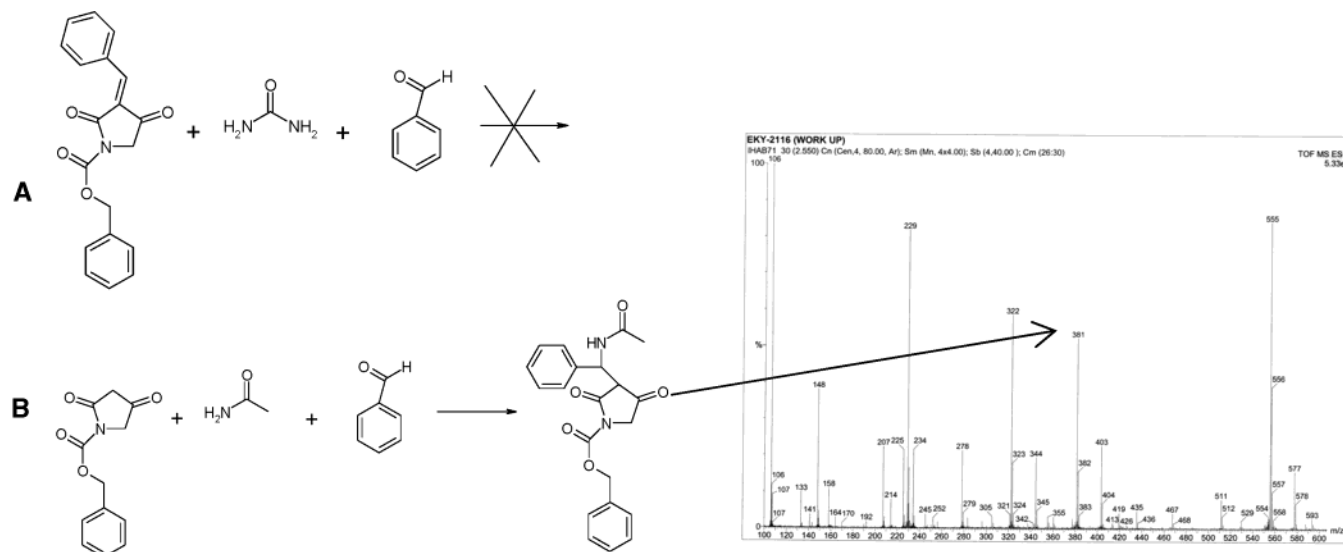
Figure 4. Mechanistic studies of the new multicomponent MCR4 reaction.
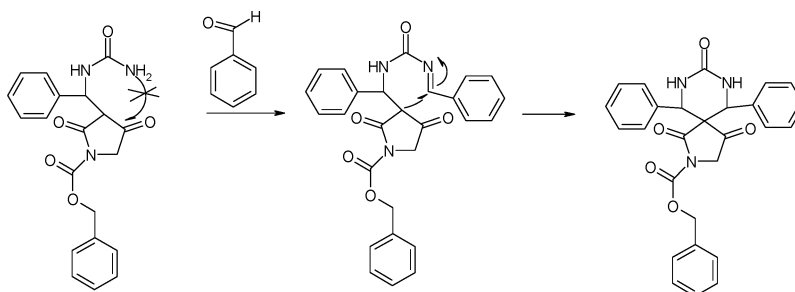

Figure 5. Proposed mechanism for the MCR4 reaction.

aliphatic aldehydes generate Schiff bases with urea that can undergo isomerization to relatively more stable enamides (see Scheme 2). These enamides are unreactive with respect to the desired multicomponent reaction or regular Biginelli reaction. This enamide forms a six-member ring sideproduct by cyclization between a double Schiff base/enamide formed between urea and 2 equiv of the aldehyde that we have observed and characterized (see product **4a** in Scheme 2):

We also performed the reaction with isovaleraldehyde (see products **4a/b** in Scheme 2) and isolated **4a** as the main product in this reaction (see Figure 4). The desired product **4b** was characterized without isolation using HPLC/QTOF-MS (see Supporting Information). After rigorous search using the Scifinder database, we did not find a precedent linking poor Biginelli reaction and the generation of this side product. We did find one report on the reaction between urea and acetaldehyde yielding a similar product.[12]

These findings prompted us to perform more detailed mechanistic studies of this reaction. First, we have preformed the Knoevenagel condensation intermediate product between the lactam and benzaldehyde (see Figure 4, path a). This product is easily obtained and competes with the desired reaction. Reaction of the isolated Knovenagel product with an additional equivalent of aldehyde and urea did not react at all (data not shown). Additionally, we have performed the reaction using acetamide and iodoacetamide instead of urea and clearly identified an intermediate product obtained from condensation of one molecule of each component using mass spectra techniques (see Figure 4, path b).

Mechanistic Aspects. These two findings together with the previously postulated intermediate for the regular Biginelli reaction[13] suggest that the mechanism of the reaction includes the reaction of a Shiff base first formed between the urea and the aldehyde with the β-ketolactam (*N*-acyliminium ion intermediate). The pending (tethered) β-ketone cannot react with the second amide from the urea as result of conformational constrain or the preponderant presence of the enol form. Instead, it is condensed with a second equivalent of the aldehyde to give the Schiff base which undergoes the same process with the second acidic proton of the lactam, affording the spirobicyclic scaffold (Figure 5). In agreement with the regiospecific generation of the syn isomers, this mechanism precludes the formation of anti isomers if both condensations proceed (almost) simultaneously.

Conclusions

In this work, we have extended the scope of a MCR4 multicomponent reaction we presented in previous literature.[1] Together with these extensions, we have studied some mechanistic aspects of the reaction and could learn more about the well-known Biginelli reaction. We have identified an important intermediate resulting from the condensation of acetamide with the corresponding β-ketolactam and aldehyde, which confirms the mechanism previously proposed by Kappe and others who have postulated a *N*-acyliminium ion intermediate for the regular Biginelli reaction. Additionally, we identified a new reaction pathway

using aliphatic aldehydes bearing α protons. This side condensation between 2 equiv of the aldehyde and 1 of urea is a significant reason for the poor yields obtained in the MCR4 new condensation with aliphatic aldehyde and, so far, in the regular Biginelli reaction when the aldehydes are aliphatic. During the preparation of this manuscript, another interesting extension based on our previous report[1,2] was proposed by Abelman et al.,[14] who used cyclopentane-1,3-dione as Meldrum's precursor.

Extensions of the reaction presented herein and the biological evaluation of the new products will be discussed elsewhere.

Experimental Section

Materials and Methods. Reagents were purchased from Aldrich and used without further purification. All solvents were analytically pure grade and were used without further purification. Analytical HPLC was were performed on a Waters Gradient System equipped with a Waters 717-Plus autosampler, a Waters 600 intelligent pump, a Waters 996 photodiode array detector, and the system was piloted with Millenium software from Waters. Mobile phases were (A) H_2O (0.1% TFA) and (B) MeCN (0.08% TFA). Separation conditions were as follows: column C18 218TP54 from Vydac, gradient a [A/B]: 3 min [100/0], 3−35 [0/100], 35−40 [0/100], flow = 1 mL/min. Gradient b [A/B]: 3 min [65/35], 3−20 [60/40], 20−30 [40/60], 30−40 [0/100], flow = 1 mL/min.

Preparative HPLC was performed on a Delta Prep Waters-4000 equipped with a Waters 486 UV tunable detector and piloted with Data-Apex software. Purifications were pre-formed on an Inertsil silica column 50 × 250 mm from GL Sciences Inc. with mobile phases (A) CHCl₃ and (B) MeOH. Separation conditions were as follows: column [A/B], 5 min [100/0], 5−35 [95/5], 35−40 [92/8], flow = 80 mL/min.

NMR and MS were carried out at the Structural Analysis Department of Bar-Ilan University. ¹H NMR spectra was recorded on Brucker DPX-300 and DMX-600 MHz spectrometers. Samples were dissolved in trifluoroacetic acid. Chemical shifts are in parts-per-million relative to TMS internal standard. Mass spectra were carried out with a Q-TOF micro, Micromass U.K. (Waters) equipped with a HPLC Separation Module 2695, a dual absorbance UV detector 2487, and an autosampler 2695 from Waters. High-resolution mass spectra were carried out on a VG Autospec by the LSIMS technique equipped with a cesium cannon; the matrix was a mixture of glycerol and thioglycerol or nitrobenzyl alcohol (FABMS).

General Synthesis of Protected β-Ketolactams. Lactams derived from (Z)-Gly, (Z)-Ala, and (Z)-Phe were synthesized by a modified method based on a previously reported procedure:[10] the thermal cyclization of the intermediate condensed products was performed in a 2-fold diluted solution of ethyl acetate, as compared to the reported method. This modified procedure precluded purification and resulted in a 90% yield of crude products that were used in the reaction. In a new procedure presented here, we have obtained cleaner lactams, as observed by HPLC. Briefly, (Z)-amino acid (3.34 mmol) and DMAP (9.33 mmol) were

dissolved in 20 mL of dry THF, to which bis(trichloromethyl)carbonate (BTC) (1.11 mmol) was added to give a white suspension. After 1 min, Meldrum's acid (3.33 mmol) was added to the suspension at room temperature. The pH was maintained between 8 and 9 with DMAP, and the resulting mixture was stirred for 3 h. The mixture were diluted with 200 mL of ethyl acetate and washed with 5% aqueous potassium hydrogen sulfate (100 mL × 2), water, and brine. The organic layer was dried, concentrated to 100 mL, and heated at reflux for 45 min. The solution was cooled to room temperature and evaporated to give an oil. Yields were ∼3.1 mmol (93%). NMR are shown in the Supporting Information.

General Procedure for the Synthesis of All the Products Using a Radley's Carousel Station. To a solution of urea (0.927 g, 15.45 mmol) and aldehyde (15.45 mmol) in 15 mL of acetic acid was added the corresponding lactam (6.48 mmol). The mixture was heated at 60−80 °C under stirring for 3h. The solution was cooled, and CH_2Cl_2 was added, followed by aqueous sodium hydrogen carbonate (pH = 8); the CH_2Cl_2 layer was separated, and the aqueous layer was extracted with extra CH_2Cl_2. The extracts were combined and washed with aqueous sodium meta-bisulfite to eliminate aldehyde excess. The organic layer was dried and evaporated to dryness. Normal-phase chromatography of the residues provided white crystalline products (50−80% yield).

Physical Data for Products (also See Supporting Information). Products 1a and 1a′. These products were isolated as a mixture 3:1 (**1a/1a′**), HPLC (method a) $R_t =$ 26.52 min (**1a**). R_t = 26.72 min (**1a′**). MH⁺ 470. HRMS calcd for $C_{27}H_{23}N_3O_5$, 469.1637; found, 469.1623. ¹H NMR (300 MHz, TFA-*d*) for **1a**: δ 7.15−7.45 (m, 15H, *Ph*CH, *Ph*CH₂O), 5.34 (s, 2H, Ph*CH₂*O), 5.16 (s, 2H, Ph*CH*), 3.2 (s, 2H). For **1a′**: δ 7.15−7.45 (m, 15H, *Ph*CH, *Ph*CH₂O), 5.27 (s, 2H, Ph*CH₂*O), 5.15 (s, 2H, Ph*CH*), 3.35 (s, 2H).

Products 1b and 1b′. These products were isolated as a mixture 3:1 (**1b/1b′**) with no discriminated peaks in HPLC. HPLC (method a) R_t = 28.93 min. MH⁺ 540. HRMS calcd for $C_{22}H_{23}N_3O_5Cl_2$, 539.1014; found, 539.0966. ¹H NMR (300 MHz, TFA-*d*) δ for **1b**: 7.15−7.45 (m, 13H, *ρ*-Cl*Ph*CH, *Ph*CH₂O), 5.58 (s, 2H, Ph*CH₂*O), 5.46 (s, 2H, Ph*CH*), 3.47 (s, 2H). For **1b′**: δ 7.15−7.45 (m, 13H, *ρ*-Cl*Ph*CH, *Ph*CH₂O), 5.70 (s, 2H, Ph*CH₂*O), 5.24 (s, 2H, Ph*CH*), 3.67 (s, 2H).

Products 1c and 1c′. These products were isolated as a mixture 3:2 (**1c/1c′**), HPLC (method a) R_t = 28.42 min (**1c**), R_t = 28.72 min (**1c′**). MH⁺ 498. HRMS calcd for $C_{29}H_{27}N_3O_5$, 497.1950; found, 497.1880. ¹H NMR (300 MHz, TFA-*d*) δ for **1c**: 7.15−7.45 (m, 13H, *ρ*-CH₃*Ph*CH, *Ph*CH₂O), 5.31 (s, 2H, Ph*CH₂*O), 5.20 (s, 2H, Ph*CH*), 3.23 (s, 2H), 2.30 (s, 6H, *ρ*-CH₃PhCH). For **1c′**: 7.15−7.45 (m, 13H, *ρ*-CH₃*Ph*CH, *Ph*CH₂O), 5.31 (s, 2H, Ph*CH₂*O), 5.24 (s, 2H, Ph*CH*), 3.27 (s, 2H), 2.30 (s, 6H, *ρ*-CH₃PhCH).

Products 1d and 1d′. These products were isolated as a mixture 2:1.7 (**1d/1d′**) with no discriminated peaks in HPLC. HPLC (method a) R_t = 22.75 min. MS (MH⁺) 502. HRMS calcd for $C_{27}H_{24}N_3O_7$, 502.1614; found, 502.1661. ¹H NMR (300 MHz, TFA-*d*) δ for **1d**: 7.50−7.35 (m, 5H, *Ph*CH₂O), 7.26 and 7.23 (AA′XX′ system), 6.96 and 6.93 (AA′XX′

system), 5.30 (s, 2H, Ph*CH₂*O), 5.20 (s, 2H, Ph*CH*), 3.34 (s, 2H). For **1d′**: δ 7.50−7.35 (m, 5H, *Ph*CH₂O), 7.29 and 7.25 (AA′XX′ system), 6.96 and 6.93 (AA′XX′ system), 5.30 (s, 2H, Ph*CH₂*O), 5.25 (s, 2H, Ph*CH*), 3.46 (s, 2H).

Products 1e and 1e′. These products were isolated as a mixture 3:2(**1e/1e′**). HPLC (method a) R_t = 26.79 min (**1e**), R_t = 27.00 min (**1e′**). MH⁺ 530. HRMS calcd for C₂₉H₂₇N₃O₇, 529.1849; found, 529.1781. ¹H NMR (300 MHz, TFA-*d*) δ for **1e**: 6.9−7.45 (m, 13H, *ρ*-OCH₃*Ph*CH, *Ph*CH₂O), 5.32 (s, 2H, Ph*CH₂*O), 5.22 (s, 2H, Ph*CH*), 3.90 (s, 6H, *ρ-OCH₃*-PhCH), 3.31 (s, 2H). For **1e′** 76.9−7.45 (m, 13H, *ρ*-OCH₃-*Ph*CH, *Ph*CH₂O), 5.46 (s, 2H, Ph*CH₂*O), 5.24 (s, 2H, Ph*CH*), 3.90 (s, 6H, *ρ-OCH₃*PhCH), 3.44 (s, 2H).

Products 1f and 1f′. These products were isolated as a mixture 1:1(**1f/1f′**) with no discriminated peaks in HPLC. HPLC (method a) R_t = 27.26 min. MS (MH⁺) 560. HRMS calcd for C₂₇H₂₁N₅O₉, 559.1339; found, 559.1371. ¹H NMR (300 MHz, CD₃COOD) δ for **1f**: 8.183 and 8.156 (AA′XX′ system), 7.58 and 7.55 (AA′XX′ system), 7.45−7.15 (m, 5H, *Ph*CH₂O), 5.09 (s, 2H, Ph*CH₂*O), 5.36 (s, 2H, Ph*CH*), 3.24 (s, 2H). For **1f′**: δ 8.186 and 8.153 (AA′XX′ system), 7.56 and 7.54 (AA′XX′ system), 7.45−7.15 (m, 5H, *Ph*CH₂O), 5.12 (s, 2H, Ph*CH₂*O), 5.45 (s, 2H, PhCH), 3.45 (s, 2H).

Products 1g and 1g′. These products were isolated as a mixture 2:1 (**1g/1g′**) with no discriminated peaks in HPLC. HPLC (method a) R_t = 27.29 min. MH⁺ 506. HRMS calcd for C₂₇H₂₁N₃O₅F₂, 505.1449; found, 505.1446. ¹H NMR (300 MHz, TFA-*d*) δ for **1g**: 7.2−7.77 (m, 13H, *ρ*-F*Ph*CH, *Ph*CH₂O), 5.56 (s, 2H, Ph*CH₂*O), 5.43 (s, 2H, Ph*CH*), 3.51 (s, 2H). For **1g′**: 7.2−7.77 (m, 13H, *ρ*-F*Ph*CH, *Ph*CH₂O), 5.68 (s, 2H, Ph*CH₂*O), 5.48 (s, 2H, Ph*CH*), 3.65 (s, 2H).

Product 2a. This product **2a** was purified from the mixture 3:1 (**2a/2a′**) by preparative HPLC. HPLC (method b) R_t = 18.68 min. MH⁺ 484. HRMS calcd for C₂₈H₂₆N₃O₅, 484.187246; found, 484.187570. ¹H NMR (600 MHz, CDCl₃) δ 7.1−7.39 (m, 15H, *Ph*CH, *Ph*CH₂O), 6.37 and 6.28 (s, 1H each, HN), 5.15 and 5.12 (ABq, 1H each, *J* = 13.5 Hz, Ph*CH₂*O), 5.11 and 5.00 (s, 1H each, Ph*CH*), 2.96 (q, 1H, *J* = 7 Hz, CH₃*CH*), 0.28 (d, 3H, *J* = 7 Hz, *CH₃*CH). ¹³C NMR (600, CDCl₃) δ 203.46, 169.33, 157, 149.49, 134.97, 134.69, 133.34, 129.74, 129.38, 129.10, 129.00, 128.61, 128.13, 127.67, 126.81, 68.41, 61.75, 60.58, 59.60, 58.68, 14.84

Product 2a′. This product was purified from the mixture 3:1 (**2a/2a′**) by preparative HPLC. HPLC (method b) R_t = 20.49 min. MH⁺ 484. HRMS calcd for C₂₈H₂₆N₃O₅, 484.187246; found, 484.187570. ¹H NMR (600 MHz, CDCl₃) δ 7.1−7.37 (m, 15H, *Ph*CH, *Ph*CH₂O), 5.84 and 5.84 (s, 1H each, HN), 5.13 and 5.04 (ABq, 1H each, *J* = 13 Hz, Ph*CH₂*O), 5.03 and 5.00 (s, 1H each, PhCH), 3.21 (q, 1H, *J* = 7 Hz, CH₃CH), 0.44 (d, 3H, *J* = 7 Hz, CH₃CH). ¹³C NMR (600, CDCl₃) δ 206.80, 165.91, 155.91, 149.97, 134.87, 134.73, 133.49, 129.97, 129.83, 129.27, 129.192, 128.60, 128.49, 128.19, 128.03, 126.88, 68.27, 61.37, 60.29, 61.81, 59.30, 15.16.

Product 2b. This product was purified from the mixture 3.5:1 (**2b/2b′**) by preparative HPLC. HPLC (method b) R_t = 33.20 min. MS (MH⁺) 552. HRMS calcd for C₂₈H₂₄N₃O₅-Cl₂, 552.109302; found, 552.1054858. ¹H NMR (300 MHz,

CDCl₃) δ 7.1−7.45 (m, 13H, *ρ*-Cl*Ph*CH, *Ph*CH₂O), 6.85 and 6.78 (s, 1H each, HN), 5.24 and 5.17 (ABq, 1H each, *J* = 12.5 Hz, Ph*CH₂*O), 4.96 and 4.83 (s, 1H each, *ρ*-ClPhCH), 3.05 (q, 1H, *J* = 7 Hz, CH₃CH), 0.40 (d, 3H, *J* = 7 Hz, CH₃CH).

Product 2b′. This product was purified from the mixture 3.5:1 (**2b/2b′**) by preparative HPLC. HPLC (method b) R_t = 33.71 min. MS (MH⁺) 552. HRMS calcd for C₂₈H₂₄N₃O₅-Cl₂, 552.109302,; found, 552.1054858. ¹H NMR (300 MHz, CDCl₃) δ 7.1−7.45 (m, 13H, *ρ*-Cl*Ph*CH, *Ph*CH₂O), 6.50 and 6.40 (s, 1H each, HN), 5.20 and 5.05 (ABq, 1H each, *J* = 12.5 Hz, Ph*CH₂*O), 4.88 and 4.85 (s, 1H each, *ρ*-ClPhCH), 3.25 (q, 1H, *J* = 7 Hz, CH₃CH), 0.57 (d, 3H, *J* = 7 Hz, CH₃CH).

Product 2c. This product was purified from the mixture 3:1 (**2c/2c′**) by preparative HPLC. HPLC (method b) R_t = 31.34 min. MS (MH⁺) 512. HRMS calcd for C₃₀H₃₀N₃O₅, 512.218546; found, 512.220300. ¹H NMR (300 MHz, CDCl₃) δ 7.1−7.45 (m, 5H, *Ph*CH₂O), 7.19 and 7.13 (AA′XX′ system), 7.08 and 6.94 (AA′XX′ system), 6.75 and 6.65 (s, 1H each, HN), 5.25 and 5.15 (ABq, 1H each, *J* = 13.5 Hz, Ph*CH₂*O), 4.95 and 4.75 (s, 1H each, *ρ*-CH₃PhCH), 2.94 (q, 1H, *J* = 7 Hz, CH₃CH), 2.29 and 2.22 (s, 3H each, *ρ*-CH₃PhCH), 0.30 (d, 3H, *J* = 7 Hz, *CH₃*CH).

Product 2c′. This product was purified from the mixture 3:1 (**2c/2c′**) by preparative HPLC. HPLC (method b) R_t = 32.89 min. MS (MH⁺) 512. HRMS calcd for C₃₀H₃₀N₃O₅, 512.218546; found, 512.220300. ¹H NMR (300 MHz, CDCl₃) δ 7.33 (m, 5H, *Ph*CH₂O), 7.22 and 7.10 (AA′XX′ system), 7.09 and 6.89 (AA′XX′ system), 6.05 (s, 2H, HN), 5.12 and 4.99 (ABq, 1H each, *J* = 12.4 Hz, Ph*CH₂*O), 4.91 and 4.87 (s, 1H each, *ρ*-CH₃Ph*CH*), 3.22 (q, 1H, *J* = 7 Hz, CH₃*CH*), 2.27 and 2.18 (s, 3H each, *ρ*-CH₃PhCH), 0.48 (d, 3H, *J* = 7 Hz, *CH₃*CH).

Products 2d and 2d′. These products were isolated as a mixture 3:1 (**2d/2d′**), HPLC (method b) R_t = 5.29 min (**2d**). R_t = 5.57 min (**2d′**). MS (MH⁺) 515. HRMS calcd for C₂₈H₂₅N₃O₇, 515.169251; found, 515.171842. ¹H NMR (300 MHz, CD₃OD) δ for **2d**: 7.42−7.25 (m, 5H, *Ph*CH₂O), 7.08 and 6.72 (AA′XX′ system), 7.03 and 6.65 (AA′XX′ system), 5.18 and 5.13 (ABq, 1H each, *J* = 12.0 Hz, Ph*CH₂*O), 5.08 and 4.99 (s, 1H each, *ρ*-OHPh*CH*), 3.10 (q, 1H, *J* = 6.5 Hz, CH₃*CH*), 0.43 (d, 3H, *J* = 6.5 Hz, *CH₃*CH). For **2d′**: 3.28 (q, 1H, *J* = 6.5 Hz, CH₃*CH*), 0.50 (d, 3H, *J* = 6.5 Hz, *CH₃*CH).

Product 2e. This product was purified from the mixture 2.5:1 (**2e/2e′**) by preparative HPLC. HPLC (method b) R_t = 20.63 min. MS (MH⁺) 544. HRMS calcd for C₃₀H₃₀N₃O₇, 544.208376; found, 544.202000. ¹H NMR (300 MHz, CDCl₃) δ 7.33 (m, 5H, *Ph*CH₂O), 7.23 and 6.85 (AA′XX′ system), 7.14 and 6.70 (AA′XX′ system), 6.52 and 6.38 (s, 1H each, HN), 5.20 and 5.13 (ABq, 1H each, *J* = 12.0 Hz, Ph*CH₂*O), 4.94 and 4.82 (s, 1H each, *ρ*-OCH₃Ph*CH*), 3.76 and 3.70 (s, 3H each, *ρ*-OCH₃PhCH) 3.05 (q, 1H, *J* = 7 Hz, CH₃*CH*), 0.40 (d, 3H, *J* = 7 Hz, *CH₃*CH).

Product 2e′. This product was purified from the mixture 2.5:1 (**2e/2e′**) by preparative HPLC. HPLC (method b) R_t = 23.26 min. MS (MH⁺) 544. HRMS calcd for C₃₀H₃₀N₃O₇, 544.208376; found, 544.202000. ¹H NMR (300 MHz,

CD$_3$OD) δ 7.40−7.25 (m, 5H, *Ph*CH$_2$O), 7.20 and 6.82 (AA′XX′ system), 7.10 and 6.66 (AA′XX′ system), 5.15 and 5.07 (ABq, 1H each, J = 12.0 Hz, Ph*CH$_2$*O), 4.95 and 4.92 (s, 1H each, ρ-OCH$_3$Ph*CH*), 3.73 and 3.65 (s, 3H each, ρ-*OCH$_3$*PhCH), 3.24 (q, 1H, J = 9 Hz, CH$_3$*CH*), 0.45 (d, 3H, J = 9 Hz, *CH$_3$*CH).

Products 2f and 2f′. These products were isolated as a mixture 2:1(**1f/1f′**) with no discriminated peaks in HPLC. HPLC (method b) R_t = 23.60 min. MS (MH$^+$) 574. HRMS calcd for C$_{28}$H$_{24}$N$_5$O$_9$, 574.15740; found, 574.156336. ^{1}H NMR (300 MHz, CD$_3$OD) δ for **2f**: 8.23 and 7.55 (AA′XX′ system), 8.00 and 7.42 (AA′XX′ system), 7.42−7.25 (m, 5H, *Ph*CH$_2$O), 5.38 and 5.27 (s, 1H each, ρ-NO$_2$Ph*CH*), 5.17 and 5.12 (ABq, 1H each, J = 13.5 Hz, Ph*CH$_2$*O), 3.05 (q, 1H, J = 7 Hz, CH$_3$*CH*), 0.35 (d, 3H, J = 7 Hz, *CH$_3$*CH). For **2f′**: 3.24 (q, 1H, J = 7 Hz, CH$_3$*CH*), 0.50 (d, 3H, J = 7 Hz, *CH$_3$*CH).

Products 2g and 2g′. These products were isolated as a mixture 2:1 (**2g/2g′**). HPLC (method b) R_t = 24.55 min (2g). R_t = 26.16 min (**2g′**). MS (MH$^+$) 520. HRMS calcd for C$_{28}$H$_{24}$N$_3$O$_5$F$_2$, 520.169159; found, 520.16840. ^{1}H NMR (300 MHz, CDCl$_3$) δ for **2g**: 6.8−7.45 (m, 13H, ρ-F*Ph*CH, *Ph*CH$_2$O), 5.24 and 5.17 (ABq, 1H each, J = 12.5 Hz, Ph*CH$_2$*O), 4.96 and 4.83 (s, 1H each, ρ-FPh*CH*), 3.05 (q, 1H, J = 6.6 Hz, CH$_3$*CH*), 0.42 (d, 3H, J = 6.6 Hz, *CH$_3$*CH). For **2g′**: 3.27 (q, 1H, J = 6.6 Hz, CH$_3$*CH*), 0.54 (d, 3H, J = 6.6 Hz, *CH$_3$*CH).

Product 3a. This product was purified from the mixture 1:1 (**3a/3a′**) by preparative HPLC. HPLC (method a) R_t = 29.65 min. MS (MH$^+$) = 560. HRMS calcd for C$_{34}$H$_{29}$N$_3$O$_5$, 559.2107; found, 559.2098. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.70−7.53 (m, 20H, *Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 6.57 and 6.31 (s, 1H each, HN), 5.05 and 4.90 (s, 1H each, Ph*CH*), 4.95 and 4.53 (ABq, 1H each, J = 11.5 Hz, Ph*CH$_2$*O), 3.2 (t, 1H, J = 7 Hz, PhCH$_2$*CH*), 1.6 (dd, 1H, J = 13.5, 7 Hz, Ph*CH$_2$*CH), 1.4 (dd, 1H, J = 13.5, 7 Hz, Ph*CH$_2$*CH).

Product 3a′. This product was purified from the mixture 1:1 (**3a/3a′**) by preparative HPLC. HPLC (method a) R_t = 30.0 min. MS (MH$^+$) = 560. HRMS calcd for C$_{34}$H$_{29}$N$_3$O$_5$, 559.2107; found, 559.2098. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.7−7.53 (m, 20H, *Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.78 and 5.75 (s, 1H each, HN), 4.92 and 5.04 (s, 1H each, Ph*CH*), 4.81 and 4.94 (ABq, 1H each, J = 11.5 Hz, Ph*CH$_2$*O), 3.42 (dd, 1H, J = 5.65, 8.5 Hz, PhCH$_2$*CH*), 1.95 (dd, 1H, J = 13.0, 5.65 Hz, Ph*CH$_2$*CH), 1.50 (dd, 1H, J = 13.0, 8.5 Hz, Ph*CH$_2$*CH).

Products 3b and 3b′. These products were isolated as a mixture 2:1 (**3b/3b′**), with no discriminated peaks in HPLC. HPLC (method a) R_t = 31.74 min. MS (MH$^+$) 628. HRMS calcd for C34H28N3O5Cl2, 628.1406; found, 628.1439. ^{1}H NMR (300 MHz, CD$_3$COOD) δ for **3b**: 7.44−6.6 (m, 18H, ρ-OCH$_3$*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.33 and 5.16 (s, 1H each, ρ-ClPh*CH*), 5.00 and 4.76 (ABq, 1H each, J = 11.5 Hz, Ph*CH$_2$*O), 3.35 (dd, 1H, J = 6, 7.5 Hz, PhCH$_2$*CH*), 1.82 (dd, 1H, J = 13, 6 Hz, Ph*CH$_2$*CH), 1.66 (dd, 1H, J = 13, 7.5 Hz, Ph*CH$_2$*CH). For **3b′**: 7.44−6.6 (m, 18H, ρ-OCH$_3$-*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.13 and 5.05 (s, 1H each, ρ-ClPh*CH*), 5.04 and 4.93 (ABq, 1H each, J = 11.5 Hz, Ph*CH$_2$*O), 3.55 (dd, 1H, J = 5, 8 Hz, PhCH$_2$*CH*), 2.15 (dd,

1H, J = 13.5, 5 Hz, Ph*CH$_2$*CH), 1.66 (dd, 1H, J = 13.5, 8 Hz, Ph*CH$_2$*CH).

Product 3c. This product was purified from the mixture 1:1 (**3c/3c′**) by preparative HPLC. HPLC (method a) R_t = 31.31 min. MS (MH$^+$) = 588. HRMS calcd for C$_{36}$H$_{33}$N$_3$O$_5$, 587.2420; found, 587.2453. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.1−7.39 (m, 18H, ρ-CH$_3$*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.75 and 5.95 (s, 1H each, HN), 5.04 and 5.23 (s, 1H each, ρ-CH$_3$-Ph*CH*), 4.61 and 4.97 (ABq, 1H each, J = 11.5 Hz, Ph*CH$_2$*O), 3.25 (t, 1H, J = 7 Hz, PhCH$_2$*CH*), 2.30 and 2.15 (s, 3H each, ρ-*CH$_3$*PhCH), 1.6 (m, 2H, Ph*CH$_2$*CH).

Product 3c′. This product was purified from the mixture 1:1 (**3c/3c′**) by preparative HPLC. HPLC (method a) R_t = 31.76 min. MS (MH$^+$) = 588. HRMS calcd for C$_{36}$H$_{33}$N$_3$O$_5$, 587.2420; found, 587.2453. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.1−7.39 (m, 18H, ρ-CH$_3$*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$), 5.75 and 5.95 (s, 1H each, HN), 5.04 and 5.23 (s, 1H each, ρ-CH$_3$-Ph*CH*), 4.61 and 4.97 (ABq, 1H each, J = 11.5 Hz, Ph*CH$_2$*O), 3.45 (dd, 1H, J = 6, 8.5 Hz, PhCH$_2$*CH*), 2.30 and 2.15 (s, 3H each, ρ-*CH$_3$*PhCH), 2.02 (dd, 1H, J = 6, 13.5, Ph*CH$_2$*CH), 1.54 (dd, 1H, J = 6, 13.5, Ph*CH$_2$*CH).

Product 3d. This product was purified from the mixture 1.25:1 (**3d/3d′**) by preparative HPLC. HPLC (method b) R_t = 32.91 min. MS (MH$^+$) 620. HRMS calcd for C$_{36}$H$_{34}$N$_3$O$_7$, 620.2396; found, 620.2331. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44−6.6 (m, 18H, ρ-OCH$_3$*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.76 and 5.52 (s, 1H each, HN), 5.20 and 5.02 (s, 1H each, ρ-OCH$_3$Ph*CH*), 4.98 and 4.66 (ABq, 1H each, J = 11 Hz, Ph*CH$_2$*O), 3.75 and 3.64 (s, 3H each, ρ-*OCH$_3$*PhCH), 3.31 (t, 1H, J = 7 Hz, PhCH$_2$*CH*), 1.65 (d, 2H, J = 7 Hz, Ph*CH$_2$*-CH).

Product 3d′. This product was purified from the mixture 1.25:1 (**3d/3d′**) by preparative HPLC, HPLC (method b) R_t = 33.83 min. MS (MH$^+$) 620. HRMS calcd for C$_{36}$H$_{34}$N$_3$O$_7$, 620.2396; found, 620.2331. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44−6.5 (m, 18H, ρ-OCH$_3$*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.25 (s, 2H, HN), 5.05 and 4.95(ABq, 1H each, J = 11 Hz, Ph*CH$_2$*O), 5.01 and 4.93 (s, 1H each, ρ-OCH$_3$Ph*CH*), 3.78 and 3.64 (s, 3H each, ρ-*OCH$_3$*PhCH), 3.48 (dd, 1H, J = 6, 8.5 Hz, PhCH$_2$*CH*), 2.11 (dd, 1H, J = 6, 14 Hz, Ph*CH$_2$*-CH), 1.6 (dd, 1H, J = 8.5, 14 Hz, Ph*CH$_2$*CH).

Product 3e and 3e′. These products were isolated as a mixture 1.4:1(**3e/3e′**) with no discriminated peaks in HPLC. HPLC (method a) R_t = 30.15 min. MS (MH$^+$) = 650, calcd 650. ^{1}H NMR (300 MHz, CDCl$_3$) δ for **3e**: 6.6−8.4 (m, 18H, ρ-NO$_2$*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 5.10 and 5.26 (s, 1H each, ρ-NO$_2$Ph*CH*), 4.76 and 5.03 (ABq, 1H each, J = 12 Hz, Ph*CH$_2$*O), 3.23 (m, 1H, PhCH$_2$*CH*), 1.77 (m, 2H, Ph*CH$_2$*CH). For **3e′**: 3.38 (m, 1H, PhCH$_2$*CH*), 2.22 (m, 2H, Ph*CH$_2$*CH), 1.64 (m, 2H, Ph*CH$_2$*CH).

Products 3f and 3f′. These products were obtained as a mixture 2:1 (**3f/3f′**) with no discriminated peaks in HPLC. Product 3f was isolated after crystallization from hot toluene. The remaining toluene solution was evaporated and after preparative HPLC, a 1:1 mixture of **3f/3f′** was obtained. HPLC (method a) R_t = 30.74 min. MS (MH$^+$) = 596. HRMS calcd for C$_{34}$H$_{27}$N$_3$O$_5$F$_2$, 595.1918; found, 595.1874. ^{1}H NMR (300 MHz, CDCl$_3$) δ for **3f**: 6.5−7.5 (m, 18H, ρ-F*Ph*CH, *Ph*CH$_2$O, *Ph*CH$_2$CH), 6.61 and 6.73 (s, 1H each,

HN), 5.94 and 5.10 (s, 1H each, ρ-FPhCH), 4.65 and 4.97 (ABq, 1H each, $J = 12$ Hz, PhCH_2O), 3.26 (t, 1H, $J = 7.3$ Hz, PhCH_2CH), 1.66 (m, 2H, PhCH_2CH). ^{1}H NMR (300 MHz, CDCl$_3$) δ for **3f′**: 6.5−7.5 (m, 18H, ρ-FPhCH, PhCH$_2$O, PhCH$_2$CH), 6.34 and 6.37 (s, 1H each, HN), 4.53 and 4.89 (s, 1H each, ρ-FPhCH), 4.90 and 4.98 (ABq, 1H each, $J = 12$ Hz, PhCH_2O), 3.44 (dd, 1H, $J = 5.2, 8.7$ Hz, PhCH_2CH), 2.10 (dd, 1H, $J = 5.2, 14$ Hz, PhCH_2CH), 1.63 (m, 1H, PhCH_2CH).

Products 4a and 4b. Urea, isovaleraldehyde and β-ke-tolactam derived from alanine were reacted as described in the general procedure of the multicomponent reaction. The crude product was analyzed with HPLC/MS chromatography, which revealed the presence of the expected spirolactam **4b** ($R_t = 17.25$ min with MH$^+ = 444$) and the presence of another product, **4a** ($R_t = 11.62$ min with MH$^+ = 197$). The reaction mixture was treated similarly to the other reactions, and after normal phase preparative HPLC, product **4a** was isolated in 50% yield. None of the desired **4b** product could be isolated. HPLC/MS conditions: Mobile phases were (A) [95% H$_2$O, 0.1% HCOOH) + 5% CH$_3$CN] and (B) MeCN. Separation conditions were as follows: 3.0×100 mm column XterraRP$_{18}$ 3.5 mm from water. Gradient [A/B]: 0.0 min [80/20], 0−20 [50/50], 20−40 [0/100], flow = 0.3 mL/min. R_t **4a** = 11.62 min. MH$^+$ = 197. R_t **4b** = 17.25 min. MH$^+$ = 444. NMR for **4a**:^{1}H NMR (600 MHz, CDCl$_3$) δ 8.24 (HN−CH=C), 6.75 (HNCH), 5.70 (d, 1H, $J = 4$ Hz, HN−CH=C), 3.77 (dt, 1H, $J = 10, 2.5$ Hz, 1H, CHCH$_2$-CH(CH$_3$)$_2$), 2.08 (m, 1H, CH(CH$_3$)$_2$), 1.70 (m, 1H, d, 3H each, CH(CH_3)$_2$), 1.4 (ddd, 1H, $J = 14, 10. 3.5$, CHCH_2-CH(CH$_3$)$_2$), 1.1 (m, 1H, CHCH_2CH(CH$_3$)$_2$), 0.94 and 0.91 (d, 3H each, $J = 7$ Hz, CH(CH_3)$_2$), 0.81 and 0.80 (d, 3H each, $J = 3$ Hz, CHCH$_2$CH(CH_3)$_2$). ^{13}C NMR (600 MHz, CDCl$_3$) δ 156.44, 120.73, 117.49, 50.85, 44.52, 23.70, 22.99, 22.97, 22.19, 21.33, 20.40.

Supporting Information Available. Physical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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